Appln No.: 09/654,373
Amendment Dated: December 29, 2003
Reply to Office Action of July 28, 2003

REMARKS/ARGUMENTS

This is in response to the Office Action mailed July 28, 2003 for the above-captioned application. Reconsideration and further examination are respectfully requested.

Applicants request an extension of time sufficient to make this paper timely and enclose the fee. The Commissioner is authorized to charge any additional fees or credit any overpayment to Deposit Account No. 15-0610.

Claims 1-9 are pending in this application.

The Examiner objected to changes in paragraph at Page 10, line 21-24 as introducing new matter, either by insertion or deletion of information. Applicants have amended this paragraph again to state that "the ionizable lipid is selected such that raising the pH surrounding the small multilamellar vesicles to a pH of around 7.5 results in the release of external, non-encapsulated oligodeoxynucleotides. This description is supported in the specification as filed, notably on Page 16, lines 1-2, and in the examples where the pH is raised to a level of 7.4 to 7.6, most commonly 7.5, to release surface bound oligos. (See for example, Page 22, lines 17-20). This revision to the added material is therefore believed to be fully supported.

The Examiner also stated that the deletion of DOGS was new matter because there is inadequate evidence to establish that reciting DOGS was an error and that DOGS is not an ionizable lipid that will work in the invention. To address this point, Applicants enclose a declaration of the inventors, attesting to the fact that DOGS was included in error, and is not an ionizable lipid suitable for use in this application.

The Examiner also rejected claims 1-9 under 35 USC § 112, first paragraph, on the same basis as the new matter objection for added material. Claim 1 has been amended in the same manner as the specification, and this rejection is therefore believed to be overcome.

The Examiner has agin rejected claims 1-9 as obvious over Wheeler. The key issue here is whether or not DOGS, which is mentioned in Wheeler, and which was incorrectly included in the present application, is an ionizable lipid within the scope of the present claims. In this regard, several facts are noteworthy. First, Wheeler discloses cationic lipids, and most of these lipids, with the exception of DOGS, are permanent cations which are not ionizable. As such, these lipids retain their positive charge regardless of pH, including at physiological pH. This is important for the purposes of Wheeler, since the use for which the lipid-nucleic acid particles of that disclosure are intended is gene transfer, and as noted on page 2 of Wheeler, "cationic lipid complexes are presently the most effective generally used means of incorporating non-viral nucleic acids into cells." DOGS fits within this category because it is still charged to a

significant extent at physiological pH.

As previously noted, DOGS is a polyamine, which includes four positively charged amines. These amines each have a separate pKa value, and these values have been reported to be 10.5, 9.5, 8.4 and 5.5. Using the Henderson-Hasselbach equation,

$$pH = pKa + \log\{ [A]/[HA]\}$$

which relates the extent of ionization of an acid HA to its deprotonated form A to the pKa value and the actual pH, one can calculate the extent to which each amine is deprotonated at pH 7.5. In this case, A is actually charge neutral, and the HA species has a positive charge.

amine pKa	ratio of neutral to positive charges	excess charge type
5.5	100	neutral
8.4	.126	positive
9.5	0.01	positive
10.5	0.001	positive

Thus, at pH 7.5, nearly every molecule (99 out of 100) of DOGS will have two positive charges, and of these more than 80 will have three positive charges. In contrast, DODAP, which has a pKa of 6.7 has a ratio of neutral to positive at pH 7.5 of 6.3 and more neutral molecules than positively charged molecules at this pH. DODMA has essentially the same pKa as DODAP.

From this analysis, it can be seen that DOGS is very different from the exemplary ionizable lipids of the present invention. There is no reasonable expectation that changing the pH to 7.5 would result in release of anionic oligodeoxynucleotides from a DOGS lipid particle to any substantial extent, since approximately 75% of the positive charge is still present. Thus, a person skilled in the art would understand that DOGS is not a cationic lipid within the scope of the present claims and that use of DOGS and permanent cationic lipids is consistent with the Wheeler application, but does not suggest any use of a ionizable lipid as claimed herein.

As previously indicated, a terminal disclaimer will be filed upon receipt of an indication that the claims are otherwise in form for allowance.

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For these reasons, this application is now considered to be in condition for allowance and such action is earnestly solicited.

Respectfully Submitted,

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